UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/247,054	02/09/1999	MICHAEL ANTONIOU	CACO-0045	7091

7590 07/03/2002

WOODCOCK WASHBURN KURTZ
MACKIEWICZ AND NORRIS
ONE LIBERTY PLACE
46TH FLOOR
PHILADEL;PHIA, PA 19103

EXAMINER	
BAKER, ANNE MARIE	
ART UNIT	PAPER NUMBER
1632	30

DATE MAILED: 07/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/247,054	Applicant(s) ANTONIOU ET AL.	
	Examiner Anne Baker	Art Unit 1632	

-- The MAILING DATE of this communication appears n the cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-21,23 and 25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-21,23 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

The response filed April 11, 2002 (Paper No. 28) has been entered. Claims 1, 11, 12, 14, 15, and 23 have been amended. Claim 2 has been cancelled.

Claims 1, 3-21, 23, and 25 are pending in the instant application.

Applicants are advised that the interview summaries to which Applicants refer were prepared at the time the interviews were conducted. Applicants question why the interview summaries were not forwarded to them prior to the mailing of the Office Action of Paper No. 25 (mailed 9/26/01). The Examiner does not handle the mailing of papers. The Examiner can only request that an interview summary be mailed out. However, it is not unusual for the staff to mail interview summaries as attachments to the next Office Action rather than as separate mailings. Applicants seem to question the accuracy of the interview summaries, but do not specify what it is that they believe to be in error nor offer documentation of their own.

Applicants state that the prosecution of this Application has been extremely protracted. However, Applicants are reminded that, with the Declaration of Dr. Robert Crombie, filed April 6, 2001, Applicants completely reversed their position with regard to the function of the HS2 site. With the acknowledgement that the HS2 site alone is sufficient to confer tissue-specific expression, new art became applicable.

The following rejections are reiterated or newly applied and constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous office action are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-21, and 23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims have been amended to recite "a self-replicating origin of replication operative in mammalian host cells." However, while the specification provides support for the use of viral origins of replication, including those that function in mammalian host cells, the specification does not provide support for the broader scope of replication origins that are operative in mammalian host cells. This would encompass other mammalian replication origins in addition to viral replication origins. Furthermore, viral replication origins covers replication origins that function in non-mammalian cells. However, the specification does not contemplate or describe vectors that use the genus of replication origins operative in mammalian host cells. As support for the amendment, Applicants point to page 37, lines 4-14, which discusses delivery of the vectors to mammals. However, this does not constitute support for the genus of replication origins now recited in the claims. Vectors that contain viral origins of replication are appropriate for delivery to mammals and are specifically described in the specification. The specification does not contemplate or describe vectors comprising the particular genus of replication origins now recited in the claims (i.e., replication origins operative in mammalian host cells).

This is a new matter rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-21, 23, and 25 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 3-21, 23, and 25 remain indefinite in their recitation of "episomal" because the definition offered in the specification is different from that known in the art. At page 5, in the last paragraph, the specification states that "[t]he term episomal vector refers to a nucleic acid vector which may be linear or circular, and which is usually double stranded in form." However, this definition is very broad and does not include the requirement that the vector be capable of integrating into the chromosome. The art teaches that plasmids are small genetic elements that replicate autonomously in the cytoplasm of a prokaryotic or eukaryotic cell (see p. 696, Elseth et al., 1995). The art further teaches that an episome is a genetic element that can replicate autonomously in the cytoplasm of the host cell or can be inserted into the chromosome of the host cell (see p. 689, Elseth et al., 1995). Thus, plasmids with this dual replicative ability are known as episomes. Some, but not all plasmids can integrate into the chromosome, such plasmids being designated episomes. Episomes, such as the F factor, contain integration sequences that allow them to integrate into the chromosome (pp. 188-189, Elseth et al., 1995). Given the definition of "episomal" as set forth in the specification, the claims read on plasmid vectors that do not integrate into the chromosome. The specification appears to use the term "episomal" as a synonym for "plasmid."

At page 3, paragraph 7 of the response, Applicants assume that the Examiner meant the opposite of what she stated. This is incorrect. The Examiner maintains her position that given the definition of "episomal" as set forth in the specification, the claims read on plasmid vectors that do **not** integrate into the chromosome. It is clear from the context of that entire paragraph that the Examiner is arguing that the definition of "episomal" set forth in the **specification** at page 5, last paragraph, where it states that "[t]he term episomal vector refers to a nucleic acid vector which may be linear or circular, and which is usually double stranded in form," is very broad. Although the art-recognized use of the term "episomal" would

include the requirement that the vector be capable of integrating into the chromosome (i.e., the episome comprises integration sequences), the definition set forth in the **specification** assigns a much broader usage to the term "episomal vector." The claim limitations are congruent with the definition set forth in the specification. The claims do not include a limitation that the episomal DNA expression vector comprises integration sequences and the specification does not describe vectors that include integration sequences. Thus, it is maintained that the claims read on plasmid vectors that do **not** integrate into the chromosome, as well as those that do.

At page 4, paragraph 1 of the response, Applicants argue that they have amended the claims to recite that expression occurs "extrachromosomally." However, this only introduces further indefiniteness to the claims, as the art does not refer to **expression** as occurring "extrachromosomally" and therefore one of skill in the art would not understand what it means to **express** a gene of interest "extrachromosomally." Expression of a gene, at the protein level, occurs in the cytoplasm of a cell, regardless of whether the gene is located on a chromosome, plasmid, or episome, but one of skill in the art would never refer to this as "extrachromosomal" expression. Applicants are confusing the processes of DNA replication and gene expression, as evidenced in the statement that "[s]upport for this amendment can be found, for example, on page 12, lines 2-3, of the application as filed wherein it is stated that the episomal DNA **replicates** 'independent of the host cell chromosomes..." (emphasis added). However, DNA **replication** is an entirely different and separate process from gene **expression**. If Applicant wishes to add the limitation that the **vector** replicates extrachromosomally, clarifying claim language is required.

Claims 1, 3-21, 23, and 25 are indefinite in their recitation of "for expressing a gene of interest extrachromosomally" because the art does not refer to **expression** as occurring "extrachromosomally" and therefore one of skill in the art would not understand what it means to **express** a gene of interest "extrachromosomally." Expression of a gene, at the protein level, occurs in the cytoplasm of a cell, regardless of whether the gene is present on a chromosome, plasmid, or episome, but one of skill in the art

would never refer to this as "extrachromosomal" expression. Applicants confusion is evidenced in the statement that "[s]upport for this amendment can be found, for example, on page 12, lines 2-3, of the application as filed wherein it is stated that the episomal DNA **replicates** 'independent of the host cell chromosomes..." (emphasis added). However, DNA **replication** is an entirely different and separate process from gene **expression**. If Applicant wishes to add the limitation that the **vector** replicates extrachromosomally, clarifying claim language is required.

Claims 1 and 6-11 remain indefinite in their recitation of "for expressing a gene of interest in a host cell" because the structural elements recited in the claims do not include a gene of interest. Thus, it is unclear how the vector could be used to express a gene of interest in the absence of a gene of interest.

At page 4, paragraph 2 of the response, Applicants argue that Applicants have amended Claim 1 to recite "a cloning site for a gene of interest." However, this does not overcome the rejection, as the claim still does not recite a gene of interest as one of the structural elements of the vector. A cloning site is not a gene of interest.

Claims 3-5 and 23 are indefinite because they depend from Claim 2 which has been cancelled.

Claims 3 and 5 are indefinite in their recitation of "wherein the component of an LCR is a component of the β-globin LCR..." because it is unclear if Claims 3 and 5 are intended to be limited to the specific components recited therein or not. Claim 2, from which Claims 3 and 5 depend, recites that the gene of interest is operatively linked to "the LCR, or component thereof" and claims 3 and 5 recite specific components without limiting the claimed vectors to these specifically recited components. Claims 3 and 5 still allow for the vector to comprise the entire LCR rather than just the specifically recited components.

At page 5, paragraph 1 of the response, Applicants emphasize that Claim 1 recites "an LCR, **or** component thereof" and argue that it is clear that if Claims 3 and 5 recite a specific component, they are not covering the entire LCR. On the contrary, Applicants are reminded that **all** the limitations from Claim

1 are incorporated into the dependent claim. Thus, while the **LCR component** is now limited to a specific one, the entire LCR is still recited in the claim, and thus Claims 3 and 5 still cover "an LCR, **or** ..." the β-globin LCR HS3 site.

The rejection of Claims 1 and 2 under 35 U.S.C. 102(b) as being anticipated by Safaya et al. (1994) is withdrawn in view of the amendment to Claim 1 adding the limitation that the self-replicating origin of replication is operative in mammalian host cells. Claim 2 has been cancelled. Nevertheless, Applicants arguments will be fully addressed to clarify several points.

At page 5, paragraph 6 of the response, Applicants argue that the claims recite that the vector is to **replicate** in a "host cell of a specific **tissue** type." However, this simply is not true. Rather the claims recite **expressing** a gene of interest (extrachromosomally?) in a host cell of a specific tissue type. Again, Applicant is confusing **replication** of a DNA element with **expression** of a gene. DNA **replication** and gene **expression** are entirely different and separate processes.

At page 6, paragraph 1 of the response, Applicants argue that the Examiner has mischaracterized the phrase "for expressing a gene of interest in a host cell of a specific tissue type" as an intended use rather than a functional limitation.

In response to applicant's arguments, the recitation "for expressing a gene of interest in a host cell of a specific tissue type" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Applicants further argue that intended use cannot be disregarded if it results in structural differences between the claimed invention and the prior art. However, in the instant case it does not. The prior art structure is suitable for the intended use.

At page 6, paragraph 2 of the response, Applicants argue that the origin of replication used by Safaya facilitates replication only in bacteria and tissue is not made up of bacteria. Again, Applicants are confusing DNA replication and gene expression. The Safaya plasmid comprises the **human** β-globin LCR and the γ-globin gene promoter. This is sufficient to drive tissue-specific expression.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1 and 10 stand rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,022,738 (Atweh et al., 2000; filed March 3, 1995), for reasons of record advanced on pages 8-9 of Paper No. 25 (mailed 9/26/01).

At page 6, paragraph 6 of the response, Applicants argue that there is no evidence that the vectors described in Atweh function extrachromosomally. However, Atweh et al. explicitly discloses that the vectors include plasmid vectors (Column 4, lines 1-2). Plasmid vectors are extrachromosomal. Thus, the composition disclosed by Atweh et al. has all the structural elements recited in the claims. When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent. See MPEP 2112.01. Thus, the function of the LCR component is considered an inherent property of the element.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6, 8, 9, 11, 12, 13, 17, and 19-21 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,022,738 (Atweh, 2000, filed March 3, 1995) and U.S. Patent No. 5,674,703 (Woo et al., 1997, filed December 2, 1992), for reasons of record advanced on pages 9-11 of Paper No. 25 (mailed 9/26/01).

At page 7, paragraph 7 of the response, Applicants argue that Woo uses tissue-specific promoters in their episomal vectors, not LCRs. However, Atweh is cited for providing the teaching of using an LCR in a plasmid vector (see Column 4, lines 1-2 of Atweh). Woo is cited as evidence that episomal vectors having viral origins of replication were well-known in the art and that such vectors will replicate in mammalian cells (see page 10, lines 13-15 of the Office Action of Paper No. 25). The motivation for using viral origins of replication on the LCR-containing plasmid vectors of Atweh is that "[t]he skilled artisan would have wanted such gene transfer vectors for use in mammalian cells," as stated on page 10,

lines 12-13 of Paper No. 25. Thus, one of skill in the art would have been motivated to make plasmid vectors comprising an LCR and a viral origin of replication. Given that Atweh disclosed plasmid vectors comprising an LCR, one of skill in the art would have immediately recognized that to use such plasmids in mammalian cells would require an origin of replication that functioned in mammalian cells. Thus, it would have been apparent to the skilled artisan to use a viral origin of replication on the vectors so that they could be used in mammalian cells. Applicants have not addressed the stated grounds for motivation.

At page 7, paragraph 7 of the response, Applicants further argue that Atweh describes using integrating vectors. This argument has already been addressed. Atweh explicitly states that the vectors of his invention include plasmid vectors (Column 4, lines 1-2). Plasmid vectors are extrachromosomal.

At page 8, paragraph 1 of the response, Applicants argue that the Examiner has used Applicants specification as a template for picking and choosing elements from the references. However, the Examiner is not relying on Applicants' motivation for using LCRs in expression vectors. No motivation is required for using LCRs in expression vectors because such compositions **already exist in the art.** Atweh explicitly discloses plasmid vectors that contain the α-LCR. The only motivation required is the motivation for using a viral origin of replication on vectors of the type disclosed by Atweh. The skilled artisan would have have wanted to used the vectors of Atweh in mammalian cells, and therefore would have used a viral origin of replication on the vectors, given that the use of viral replication origins on episomal vectors was well-known in the art, as evidenced by Woo et al.

At page 8, paragraph 2 of the response, Applicants argue that Woo defines episomal transformation as "stable transformation" and therefore there is no motivation to combine Woo with Atweh. However, the stated grounds of motivation for using a viral origin of replication on the vectors of Atweh is to be able to use the vectors for gene transfer in mammalian cells. Applicants have not addressed the stated grounds of motivation.

At page 8, paragraph 3 of the response, Applicants argue that the art did not disclose or suggest the combination of LCRs with episomal vectors, nor was there motivation to do so. Applicants further argue that the Declaration of Dr. Michael Antoniou states that there was simply no motivation to combine the concepts. However, **such compositions already existed in the art** at the time of Applicants' filing. No motivation is required to combine anything as far as using LCRs on extrachromosomal vectors goes, because Atweh already discloses LCR-containing plasmids. The Declaration has been fully considered but is not found to be persuasive.

Claims 7, 9, 18, and 19 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,022,738 (Atweh, 2000, filed March 3, 1995) and U.S. Patent No. 5,674,703 (Woo et al., 1997, filed December 2, 1992), as applied to claims 6, 8, 9, 11, 12, 13, 17, and 19-21 above, and further in view of Yates et al. (1985), for reasons of record advanced on pages 11-13 of the Office Action of Paper No. 25 (mailed 9/26/01).

At page 9, paragraph 2 of the response, Applicants argue that Yates is relied on merely for piecing together additional recitations in Claims 7, 9, 18, and 19. On the contrary, Yates is cited as evidence that the Epstein-Barr virus origin of replication is well-known in the art, since 1985, and that their use on plasmids to provide for stable replication in mammalian cells is also well-known in the art for many years, at least 14 years prior to Applicants' filing date.

Claim 23 stands rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,022,738 (Atweh, 2000, filed March 3, 1995) and U.S. Patent No. 5,674,703 (Woo et al., 1997, filed December 2, 1992), as applied to claims 6, 8, 9, 11, 12, 13, 17, and 19-21 above, and further in view of Chapman et al. (1991), for reasons of record advanced on pages 13-14 of the Office Action of Paper No. 25 (mailed 9/26/01).

At page 9, paragraph 5 of the response, Applicants incorporate their earlier arguments, that there is no motivation to combine Atweh and Woo. These arguments have already been addressed above. Applicants dismiss the use of Chapman as inappropriate hindsight reconstruction. However, Chapman et al. is only cited for its teaching that it is common practice to transfect cultured host cells for the *in vitro* expression of a protein of interest. Claim 23 is directed to using the vectors of the invention to obtain tissue-specific expression of a gene of interest, by culturing a host cell transfected with the vector. Since the vectors are either known in the art or are obvious, the claimed method is obvious.

The rejection of Claim 25 under 35 U.S.C. 103(a) is withdrawn. The Examiner agrees that the skilled artisan would not be motivated to test LCRs for their ability to confer tissue-restricted expression of a gene of interest in the context of an episomal vector using the claimed method

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker, Ph.D. whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Anne-Marie Baker, Ph.D.

Anne-Marie Baker
ANNE-MARIE BAKER
PATENT EXAMINER